REMARKS

I. Status of the application

Applicants take this opportunity to recap the circumstances leading to the filing of the present Request for Continued Examination application and accompanying Submission:

1. Applicants had filed a change of correspondence address with the Patent Office on July 1, 2004. Unfortunately, the Office Action dated July 13, 2004, still was mailed to the prior address on record and therefore never received by the undersigned. For this reason, the application was deemed abandoned for Applicants' failure to timely file a response. See the Notice of Abandonment dated January 25, 2005.

2. On August 10, 2005, Applicants successfully petitioned for withdrawal of the holding of abandonment based on U.S. PTO error. See the Decision to Grant the petition dated August 25, 2005.

3. With their Petition, Applicants also submitted an Amendment and Reply under 35 U.S.C. § 1.116 in response to the July 13, 2004, Office Action. In that amendment, Applicants canceled claims 1-47 without prejudice or disclaimer, and added claims 48-77, which comport with the subject matter of previously elected Group I.

4. The Patent Office subsequently mailed an Advisory Action on September 21, 2005, which neither entered Applicants proposed amendments of August 10th, nor their arguments in support of novelty and non-obviousness. According to the Office, Applicants' amendments raised new issues that would require further search and consideration. For these reasons, the amendments were not entered and the rejections of July 13th were maintained.

Furthermore, the Office appended a reissued copy of the July 13th action to the Advisory Action and restarted the response period as of September 19th, which Applicants understand to be the mailing date of the reissued action.

By way of this Submission, Applicants respectfully request entry of those amendments, re-presented herein, for the Office's consideration and examination.

II. Status of the claims

Claims 1-25 and 27-47 are hereby canceled without prejudice or disclaimer. Claim 26, which was withdrawn due to an earlier restriction requirement is also cancelled herewith. Applicants reserve the right to file a divisional application to the non-elected subject matter.

Claims 48-77, which comport with the subject matter of restricted Group I previously elected, are added. In general, the new claims clarify that the non-DNA adjuvant is delivered directly into cells of an individual. Claims 48-77 do not introduce new matter and find support in the application as identified by the following Table:

New claim	Basis in the application as filed
48	claims 1, 3 and 22
49	claim 2
50	claim 24
51	claim 19
52	claim 21
53	claim 25
54	claim 7
55	claim 12
56	claim 15
57	claim 16 and 33
58	claim 23
59	claim 5
60	claim 29; page 6, lines 4 to 17
61	page 6, lines 4 to 17
62	page 6, lines 4 to 12
63	claim 30; page 28, lines 13 and 14
64	page 28, lines 11 and 12
65	claim 2
66	claim 24
67	claim 19
68	claim 12
69	claim 25
70	claim 7
71	claim 12
72	claim 15
73	claim 16 and 33
74	claim 23
75	claim 5
76	claim 32
77	claim 36

New claim 48

New claim 48 specifies that the recited core carrier particles are "coated with" the recited nucleic acid molecule and non-DNA adjuvant. This qualification simply incorporates the subject matter of original claims 3 and 22. A skilled person would readily understand that such coated particles are delivered directly into cells on the basis of, for example, page 28, lines 10 to 22 of the application as filed.

New claim 60

Method claim 60 is drawn to a method for generating an immune response by co-administering the nucleic acid and non-DNA adjuvant as proposed in original claim 29 and the disclosure at page 6, lines 4 to 17 of the application. Method claims 61 and 62 recite alternative ways by which the nucleic acid and adjuvant are administered, based on the passage at page 6, lines 4 to 17 of the application as filed.

New claim 77

Claim 77 is drawn to a pharmaceutical composition comprising the coated particles of claim 48. The claim includes therefore the feature that the non-DNA adjuvant is delivered into cells of an individual for the same reasons as set out above for claim 48.

There are no counterparts to claims 6, 8-11, 13 and 14 in the newly proposed claim set. Previously, the Office required election among the following species of adjuvant used in the claimed invention: (a) protein; (b) lipid; (c) non-protein hormone; (d) vitamin; and (e) mycobacterial cell wall material.

III. Species Election

In response to this species election requirement, Applicants elected species (b), namely adjuvants that are lipids as recited in original claim 7 and now in new claim 54. It is to be understood that this election of species was for the purposes of preliminary search only, and that upon allowance of a generic claim, Applicants will be entitled to consideration of the claims to the additional species.

IV. Clarification of the claimed invention

One aspect of the present invention concerns co-administering a nucleic acid encoding an antigen and a non-DNA adjuvant directly into the cells of an individual in order to elicit an immune response. Prior to the present invention, intracellular delivery of a non-DNA adjuvant had not been contemplated. Indeed, prior to Applicants' invention, adjuvants were considered to act extracellularly and, for this reason, the skilled person delivered those adjuvants extracellularly.

The present inventors, however, have shown for the first time that a non-DNA adjuvant can be effectively delivered directly *into* cells of an individual to enhance the immune response to an antigen encoded by a coadministered nucleic acid. This technical effect is clearly demonstrated in the present Examples. In Example 1, gold beads, coated with a vector encoding carcino embryonic antigen (CEA) and MPL adjuvant, are used successfully to generate an immune response. In Examples 2-5 Quil A adjuvant is administered on gold particles which are also coated with viral antigen encoding sequences, to produce an enhanced immune response.

Thus, the invention has provided the art with a new and entirely unexpected means of enhancing an immune response.

V. Applicants have cancelled claims 1, 16, and 33-47 and, therefore, the rejection of these claims as non-enabled is moot

Claim Rejections – 35 USC § 112

The Examiner rejected claims 1, 16, and 33 to 47 under 35 USC 112, first paragraph, for lack of enablement. The new claims do not comprise claims corresponding to original claims 33 to 47 and it is assumed therefore that the Examiner's rejections in relation to those claims are now moot.

New claims 57 and 73, however, also recite an "immune shift adjuvant," but clarify that this adjuvant "is effective to enhance the T helper 1 (Th 1) component of an immune

response elicited against the antigen in an individual receiving said particles." This language is based on that which appeared in original claim 33.

In view of this, it is submitted that the Examples of the application do indeed enable the use of an immune shift adjuvant as is defined in claims 57 and 73 and that those claims are therefore enabled. It is submitted further that claims 48 and 60 are enabled too for the same reasons.

VI. Applicants have cancelled claims 1, 2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, 46, and 47 and, therefore, the rejection of these claims as allegedly anticipated by Spitler *et al.*, is moot

The Examiner rejected claims 1, 2, 7, 12, 15, 27 to 29, 33, 35, 37, 39, 41, 43, 46 and 47 under 35 USC 102(e) in view of U.S. Patent No. 5,925,362 (hereinafter "Spitler *et al.*"). Since Applicants have cancelled these claims, they consider this specific rejection moot. On the other hand, since new claims 48, 49, 54, 55, 56 and 60 correspond to certain of these rejected claims, Applicants take this opportunity to address the Examiner's remarks and allegations.

Spitler *et al.* does not disclose direct intracellular delivery of a non-DNA adjuvant in combination with a nucleic acid molecule encoding an antigen. Spitler *et al.* lists a number of formulations which may be administered to enhance an antigen response, specifically to prostate antigens (col. 7, lines 1 to 5). Spitler *et al.* does not, however, disclose any particular adjuvant in combination with DNA encoding an antigen. Indeed, even when DNA encoding antigens are disclosed, Spitler *et al.* says nothing about adjuvants (col. 8 lines 3 to 14).

Furthermore, Spitler *et al.* also is silent about directly administering a non-DNA adjuvant into cells and only contemplates parenteral or extracellular administration (col. 8). Spitler *et al.* discloses neither particles coated with a DNA encoding an antigen nor with a non-DNA adjuvant. Accordingly, Applicants consider claims 48, 49, 54, 55, 56 and 60 to be novel.

VII. Applicants have cancelled claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44, and 45 and, therefore, the rejection of these claims as allegedly rendered obvious by the cited prior art is moot

The Examiner rejected claims 1, 3-5, 17 to 25, 29-34, 36-38, 40, 42, 44 and 45 under 35 USC 103(a) as being unpatentable over Spitler *et al.* in view of Fynan *et al.*, Golding *et al.* and Sedegah *et al.* Since Applicants cancelled these claims, the rejection is moot. Nevertheless, Applicants take this opportunity to address the Examiner's allegations.

As explained in the preceding subsection, Spitler *et al.* does not disclose nor contemplate intracellular administration. There is certainly no disclosure of particles coated with DNA encoding an antigen and/or a non-DNA adjuvant.

Fynan *et al.* is concerned with DNA vaccination and describes gene gun administration of gold particles and DNA to the epidermis. However, there is no mention of the use of adjuvants of any kind. Certainly, there is no disclosure or suggestion of direct intracellular delivery of a non-DNA adjuvant with the DNA vaccines. Accordingly, it is submitted that Spitler *et al.* and Fynan *et al.* cannot be combined to arrive at subject-matter falling within the scope of the present claims. For that reason, it is submitted that the new claims cannot be obvious in view of a combination of Spitler *et al.* and Fynan *et al.*

Sedegah *et al.* teaches the adjuvant-free intramuscular injection of mice with plasmid DNA encoding the *Plasmodium yoelii* circumsporozoite protein induced higher levels of antibodies and cytotoxic T lymphocytes against the *P. yoelii* circumsporozoite protein than did immunization with irradiated sprorozoites. Clearly, there is no disclosure or suggestion of the direct intracellular delivery of a non-DNA adjuvant with the *circumsporozoite* protein. Indeed, Sedegah *et al.* report adjuvant-free immunization. Accordingly, it is submitted that Spitler *et al.*, and Fynan *et al.* and Sedegah *et al.* cannot be combined to arrive at subject-matter falling within the scope of the present claims. For that reason, it is submitted that the new claims cannot be obvious in view of a combination of those documents.

Golding *et al.* teaches the use of monophosphoryl lipid as an adjuvant to increase Th1 type immune responses. However, Golding *et al.* does not teach nor contemplate the direct intracellular delivery of a non-DNA adjuvant with a DNA vaccine. Indeed, Golding *et al.*

suggests that adjuvants influence the nature of an immune response to an antigen by stimulating different cell types including TH cells, i.e. by cell surface contact (see page 35, right hand column, final two paragraphs). Clearly there is no contemplation of direct intracellular delivery of a non-DNA adjuvant. Accordingly, it is submitted that Spitler *et al.* and Golding *et al.* cannot be combined to arrive at subject matter falling within the scope of the present claims. For that reason, it is submitted that the new claims are not obvious in view of a combination of Spitler *et al.* and Golding *et al.*

The Examiner's rejections take no account of the prevailing opinion in the art of the priority date concerning adjuvant use. In fact, given the accepted teaching in the art at the time, the modifications that are suggested would not have been routine or even technically sensible to a skilled person. Instead, making these modifications would have been akin to disregarding all existing teaching, something that the skilled person (absent extremely persuasive teaching or data) would not have done.

At the priority date, the accepted dogma in this field was that adjuvants functioned extracellularly. This is evidenced in part by the hypothesized adjuvant mechanisms, which assume extracellular function. *See*, Sasaki *et al.*, Anticancer Research 18, 3907-3916, 1998 (pages 3909-3910) (of record; see Applicants' Information Disclosure Statement dated July 8, 2003). Indeed this assumption persisted even after the priority date, at least into 2000. A number of theories of adjuvant action existed. Some adjuvants were thought to have a local effect, providing for slow sustained release of antigen. Some adjuvants were believed to improve targeting of antigen to antigen presenting cells, by converting soluble antigen to particulate form. Another possibility was that adjuvant had a systemic stimulatory effect on immunocompetent cells. Whilst DNA encoding an adjuvant (such as that in Larsen *et al.*) would need to be delivered into cells to allow expression of the active adjuvant in the first place, it was certainly not obvious to try to deliver a non-DNA adjuvant directly into a cell and still expect the adjuvant to function.

None of the cited documents provides any disclosure that would persuade the skilled person to ignore this accepted teaching. In fact, the cited documents actually support the teaching - either implicitly by always delivering adjuvant extracellularly, or explicitly (see

Sasaki *et al.* 1998 above). The documents cited in the Office Action certainly do not suggest anything of the present invention. Fynan *et al.* and Sedegah *et al.* do not use adjuvants at all, and Golding *et al.* supports extracellular delivery of an adjuvant in accordance with the prevailing dogma.

There was simply nothing in the field at the priority date that would have suggested to the skilled person even the possibility of delivering a non-DNA adjuvant directly into cells. Given the technical bias against intracellular delivery, for a skilled person to attempt this, he would have needed to have not only an explicit direction to do so, but also some indication that, against all the accepted teaching, a non-DNA adjuvant could function if delivered intracellularly. This simply was not available. As such, the presently claimed invention is a surprising departure from the previous teaching and not obvious with respect to the prior art.

VIII. Conclusion

Applicants invite the Examiner to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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